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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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VENABLE, BAETJER, HOWARD & CIVILETTI, LLP
1201 NEW YORK AVE, N.W.
SUITE 1000
WASHINGTON, DC 20005

EXAMINER

GOLDBERG, JEANINE ANNE

ART UNIT PAPER NUMBER

1634

DATE MAILED: 04/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/881,012	GINNS ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 February 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-27 is/are pending in the application.
- 4a) Of the above claim(s) 13, 14 and 27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12 and 15-26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>0103</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This action is in response to the papers filed September 20, 2002. Currently, claims 1-27 are pending. Claims 13, 14, 27 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election without traverse of Group I (Claims 1-12, 15-26) in Paper No. 15 is acknowledged.

Applicant's election of Group I in Paper No. 15 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 13-14, 27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The requirement is still deemed proper and is therefore made FINAL.

Priority

3. This application claims priority to 09/175,158, filed October 19, 1998 and provisional application 60/062,924, filed October 20, 1997.

The first line of the specification discusses related applications which are not priority documents.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Sequence Rules

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

Specifically, pages 22-23 contain sequences which are not identified by SEQ ID NO:. Appropriate correction is required.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-12, 15-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for analyzing an individual for a genotype associated with BAD in a family affected by bipolar disorder by determining a lod score of a microsatellite marker between D4S394 and DRD5, does not reasonably provide enablement for determining the genotype of any marker within any of the three recited regions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are not enabled by the specification because the specification does not provide sufficient guidance to enable the skilled artisan to determine genotype which are associated with increased or decreased resistance to bipolar affective disorder without undue experimentation for the reasons which follow.

The claims are broadly drawn to methods for determining whether a genotype is associated with increased or decreased resistance to bipolar disorder in a family by determining the genotype of a family member in the region between D4S402 and D4S424 or between D4S431 and D4S404 or between D11S394 and D11S29. The claimed method is drawn to a method of looking for markers associated with susceptibility or resistance to bipolar affective disorder (BPAD) by looking in three specifically recited regions, one on chromosome 4p, on chromosome 4q and one on chromosome 11.

The specification teaches that a genome-wide search using DNA from patients with bipolar disease was performed with 55 markers (page 34) and regions which gave lod scores higher than 2.0 were considered to be linked. Markers at S13S1 (13q13), D15S45 (15q111-qter) and D6S7 (6pter-p24) were found to have the highest statistical linkage but the specification acknowledges that none of the markers provided a lod score of 3.0 or greater. The specification then teaches that the Old Amish Order was used to perform a genetic epidemiological study of bipolar affective disorder. Genomic DNA was used from individuals from this pedigree to perform a genome wide scan and to look for evidence for regions linked to mental health wellness. The specification teaches that linkage was found with markers on 4p (D4S2949) which is located in the region previously identified by Blackwood to contain a bipolar susceptibility locus and two makers for chromosome 11q (page 44). The specification teaches that the subpedigress were genotyped using additional markers in the 4p region and linkage with mental wellness was analyzed. The specification provides Tables of data but no clear explanation that the data in the tables demonstrate that a protective allele for bipolar affective disorder lies in the 4q or 4q regions. The specification suggests that it is possible and would make sense that there are susceptibility and protective alleles but does not provide sufficient evidence to establish that such an allele exists between the recited markers.

With regard to the region on chromosome 11, the specification fails to provide the LOD score within the region. The specification teaches that "six markers showed linkage" including D11S146. The specification fails to provide any information regarding

the region between D11S394-S11S29. The art fails to teach any associations between bipolar affective disorder and markers on chromosome 11.

The evidence provided in the specification is not sufficient to enable the skilled artisan to use the claimed method because the correlation between decreased risk for BPAD and the recited markers on chromosome 4 has not been established. The specification and the paper by Ginns et al. (PNAS, Vol. 95, pages 15531-15536, December 1998) does not provide data to establish that there is predictable linkage between the regions recited in the claims. At best the specification states that there was linkage for D4S2949 on 4p and D4S397 on 4q but does not establish that markers between the recited markers are predictably linked. The art teaches that the linkage of markers to bipolar disease is highly unpredictable due to the evidence that a number of different genes appear to be involved in this disease. Berrettini (J. Affective Disorders, Vol. 50, pages 287-297, 1998) teaches that the art has given conflicting report for linkage of particular chromosomal regions and susceptibility. Berrettini also discusses that linkage may only be inferred when the LOD score is greater than 3. Berrettini discusses several linkage studies which have described linkage, however, after further analysis, the linkage has not been able to be confirmed. For example, Egeland described a linkage study of Old Order Amish pedigrees with evidence for a bipolar disorder locus on 11p15, but the finding has been weakened by failure to confirm this putative locus in other populations. Similarly, Xq28 was reported to be linked, however, independent investigators have not confirmed the Xq28 linkage (page 289, col 2). As

an example, Berrettini cite the initial linkage statistic as found in Blackwood, and the subsequent confirmation of 4p16 to satisfy generally accepted criteria for valid linkage.

The ability to screen for a wellness allele is even more unpredictable because it is very difficult to distinguish between the presence of a protective allele and the absence of a susceptibility allele. Furthermore, the claims are drawn to a method for looking for a susceptibility or a resistance genotype but the skilled artisan would be unable to predict which makers are linked to susceptibility or resistance based upon the linkage of a single marker within a large region. Extensive experimentation with no predictable results would be required of the skilled artisan to determine the markers which are associated with susceptibility or resistance to BPAD. Berrettini teaches that verification by a second investigating group is required because of the high variability in results that have been observed. Consequently, the skilled artisan would be required to perform undue experimentation to make and use the claimed method.

The specification fails to enable any marker within the recited regions. Markers as defined by the instant specification are "polymorphic locus that serves to identify a unique locus on a chromosome." Markers therefore include but are not limited to microsatellite markers, restriction fragment length polymorphisms, translocations, mutations, deletions, single nucleotide polymorphisms, for example. The skilled artisan would be required to perform additional experimentation to practice the claimed invention as broadly as claimed. While one could conduct additional experimentation to determine whether markers exist within the recited regions on chromosome 4 and 11 and these newly discovered markers are associated with BPAD, the outcome of such

research cannot be predicted, and such further research and experimentation are both unpredictable and undue. It is unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention.

Additionally, as required by the instant claims, a method for determining a genotype associated with increased or decreased resistance is not predictable given the association in a single individual. As provided by Berrettini, the testing requires large populations and confirmation. The claim appears to assert that the finding of an association in a single member of a family with bipolar affective disorder would suggest a method for determining a genotype. This method however results in unpredictable results which would require further experimentation and confirmation to obtain a reliable result for which a skilled artisan would determine a genotype with an association. Therefore, as written, the method is merely a research design which is intended to determine whether a genotype is associated with increased or decreased resistance and not directed to the result itself. The claim is merely drawn to a method which in itself requires further experimentation with unpredictable results.

Therefore, as written, the skilled artisan would be unable to practice the claimed invention as broadly as claimed with out further unpredictable experimentation.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-12, 15-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to the identification of markers which are associated with susceptibility or resistance to BPAD. The specification has provided some preliminary data that a single marker in the 4p region, and a single marker in the 4q region show some evidence for linkage to mental health wellness in the Old Amish Order. However, the claims are broadly drawn to a method of using a large genus of markers which lie in a large region of chromosome 4 and 11, but the specification does not teach that a representative number of markers in this large region are linked to BPAD. A common structural feature has not been identified such that the skilled artisan would know that all markers in this region are linked or which specific markers within the recited regions are linked.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2b 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the ‘written description’ inquiry, whatever is now claimed”. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written

description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The specification fails to describe a representative number of markers within the recited regions of chromosome 4 and 11. Moreover, the specification fails to describe a representative number of markers within the recited regions of chromosome 4 and 11 which are associated with an increased or decreased resistance to familial bipolar affective disorder. Markers as defined by the instant specification are a polymorphic locus that serves to identify a unique locus on a chromosome. Markers therefore include but are not limited to microsatellite markers, restriction fragment length polymorphisms, translocations, mutations, deletions, single nucleotide polymorphisms, for example. The specification has only described a limited number of microsatellite markers which are not all associated with BAD. The art teaches that there are about 20 cM between markers D4S402 and D4S42 and about 20 cM between markers D4S431 and D4S404. These regions are extremely large and contain millions of base pairs. The specification has not described a representative number of markers from the numerous types of markers known, such as microsatellite markers, SNPs, deletions, insertions which are associated in the very large regions on chromosomes 4 and 11.

Therefore, the specification has not sufficiently described the essential features of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 6, 7, 12, 15-19, 21-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Blackwood et al (Nature Genetics, Vol. 12, pages 427-430, April 1996).

Blackwood et al. (herein referred to as Blackwood) teaches identifying locus associated with bipolar affective disorder. Blackwood teaches carrying out a linkage study in twelve bipolar families (abstract). In a single family a genome search employing 193 markers indicated linkage on chromosome 4p where the marker D4S394 generated a two-point lod score of 4.1 (limitations of Claim 1, 6, 7, 23). Blackwood teaches eleven markers gave positive lod scores including D4S394, D4S1582, D4S1605, D4S1599 and D4S403 (page 427, col. 2, para 1). Table 1 provides a detailed analysis of various locus and the LOD scores (page 429). As described in the Methods section, bipolar families were ascertained and the bipolar status of the individuals in the family were ascertained. DNA was extracted from whole blood, amplified, and gel analysis of microsatellite was performed (page 430, col. 1)(limitations

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of Claim 12, 15, 16). The analysis was performed by analyzing allele frequencies from the family data (page 430, col. 1)(limitations of Claim 17-19, 21-22).

Conclusion

8. No claims allowable.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg
Jeanine Goldberg
April 16, 2003

Gary Benzion
GARY BENZION, Ph.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600